10/018446

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 99,423-A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/40281	International filing date *(day/month/year)* 21/06/2000	Priority date *(day/month/year)* 22/06/1999
International Patent Classification (IPC) or national classification and IPC C07H19/16		
Applicant CV THERAPEUTICS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/01/2001	12.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Jenn, T Telephone No. +49 89 2399 7348

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/40281

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

3-43	as originally filed				
1,2	as received on	28/06/2001	with letter of	26/06/2001	

Claims, No.:

1-25	as originally filed

Drawings, sheets:

1/4-4/4	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 18,20-22.

because:

   ☒ the said international application, or the said claims Nos. 20-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 18 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/40281

1. Statement

Novelty (N)	Yes:	Claims	1-17,19-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17,19-25
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17,19,23-25
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

1. The amendments filed with the letter dated June 26, 2001, received on June 28, 2001, introduce subject-matter which extend beyond the content of the application as filed, contrary to Article 34(2) PCT. The amendments concerned are the following:

1.1 Amended claim 1 **(see particularly Item VIII § 3 of this opinion)**:

A compound having the formula as claimed in claim 1, wherein R^3 is selected from "$NR^{20}C(NR^{20})NHR^{22}$" (line 7, new page 47), or wherein substituents are optionally substituted with "$NR^{20}C(NR^{20})NHR^{22}$" (line 14, new page 47) is not disclosed in the application as originally filed which discloses such a compound wherein R^3 is "$NR^{20}C(NR^{20})NHR^{23}$" (line 7, page 44), or wherein substituents are optionally substituted by "$NR^{20}C(NR^{20})NHR^{23}$" (line 14, page 44).

A compound having the formula as claimed in claim 1, wherein the substituents of R^7 are optionally substituted with "$NR^{20}C(NR^{20})NHR^{22}$" (line 13, new page 48) is not disclosed in the application as originally filed which discloses such a compound wherein substituents are optionally substituted by "$NR^{20}C(NR^{20})NHR^{23}$" (l. 11, p. 45).

1.2 Amended claim 8:

A compound according to claim 8 wherein R^7 is selected from "**C_{1-8}** alkyl that is optionally substituted with **one substituent** selected from **halo, CF_3, CN and OR^{20}**" (lines 27-28, new page 51) is not disclosed in the application as originally filed which discloses such a compound wherein R^7 is selected from "**C_{1-5}** alkyl, wherein the alkyl substituent is optionally substituted with **aryl, and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3**" (page 48, lines 22-24).

1.3 Amended claim 9:

A compound according to claim 9 wherein R^7 is selected from "**C_{1-3}** alkyl that is optionally substituted with **one substituent** selected from **halo, CF_3, CN and OR^{20}**" (lines 1-2, new page 52) is not disclosed in the application as originally filed which discloses such a compound wherein R^7 is selected from "**C_{1-5}** alkyl, wherein the alkyl substituent is optionally substituted with **aryl, and wherein each optional aryl substituent is optionally substituted with halo**" (page 48, lines 31-33).

1.4 Amended claim 16:

A compound according to claim 16 wherein R^7 is selected from "**C_{1-3}** alkyl that is optionally substituted with **one substituent** selected from **halo, CF_3, CN and OR^{20}**" (lines 11-12, new page 53) is not disclosed in the application as originally filed

which discloses such a compound wherein R^7 is selected from "**C_{1-5}** alkyl, wherein the alkyl substituent is optionally substituted with **aryl, and wherein each optional aryl substituent is optionally substituted with halo**" (page 50, lines 11-13).

1.5 Amended description:

The same as disclosed in § 1.1 above applies to the corresponding amendments in the description (new page 4, line 16; new page 5, lines 1, 13 and 25).

A compound wherein "when R^1=CH_2OH, then it is most preferred that R^7 is a methyl and R_3 is CO_2Et" (see new page 8, line 29) is not disclosed in the application as originally filed (see original claims 11 and 12 which depend on claim 10).

2. As some of the amendments of the description are not allowable (see above), and as said amendments were not made by the way of **replacement pages** in the manner stipulated by Rule 66.8(a) PCT (see as well the PCT Guidelines Chap. VI-7.2 and 7.3), certain of the allowable amendments of the description cannot be taken into consideration in this report (the numbering of the pages would become confusing).

Therefore, although the amendments of the description from new page 5 (line 27) to new page 8 (line 28), and from new page 8 (line 31) to new page 9 (line 28) do not introduce subject-matter which was not disclosed in the application as originally filed, these amendments are not taken in consideration in this report, nor are taken the allowable amendments of the description on new page 10 (lines 5 and 9), on new page 23 (line 7), on new page 25 (line 15), on new page 26 (line 5 [Obs: "is" should be replaced by "in"]), on new page 29 (line 10), on new page 30 (line 1), on new page 31 (line 1), on new page 34 (line 1), on new page 37 (line 1), and on new page 40 (line 1).

3. Therefore, the present opinion will be given on the subject-matter of claims 1-25 as originally filed, on the subject-matter of amended pages 1-2 of the description as filed with the letter dated June 26, 2001, received on June 28, 2001, which replace the original pages 1-2, and on original pages 3 to 43 of the description.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject-matter of **claim 18** is so unclear (see the grounds for this objection in

Item VIII of this opinion), that no meaningful opinion can be formed on the novelty, inventive step and industrial applicability of said claim.

2. The method as claimed in **claims 20 to 22** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (diagnostic method carried out on the living human or animal body). Consequently, **no opinion** will be formulated **on** the **industrial applicability** of the subject-matter of these claims (Article 34(4)(a)(i) PCT, see also the PCT-guidelines IV-2.4.(d) and IV-2.5); an opinion on novelty and inventive step will be given for the alleged effects of a compound of claim 1 in the method of claims 20 to 22.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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Reference is made to the following document:

D1 (R. MARUMOTO et al.: 'Synthesis and coronary vasodilating activity of 2-substituted adenosines' Chem. Pharm. Bull., vol. 23, no. 4, 1975, pages 759-774).

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1. Document **D1** (the references in parentheses applying to this document) discloses the vasodilatating (page 759, note 7, and 768, Table V, last column) 2-Substituted adenosine compounds **29j** and **29k** (page 768, Table V), which are pyrazole substituted derivatives of adenosine of the formula as disclosed in claim 1 of the application, wherein R^2 and R^4 are either both CH_3 (compound **29j**) or CH_3 and Benzyl (compound **29k**).

2. The subject-matter of claim 1 therefore **differs** from these known compounds in that either R^2 or R^4 is hydrogen (see the proviso of claim 1).

3. The subject-matter of **claim 1** is therefore **novel** (Article 33(2) PCT).

4. The **problem** to be solved by the present invention may therefore be regarded as to find alternative vasodilatating compounds.

5. The **solution** to this problem proposed in **claim 1** of the present application is considered as involving an **inventive** step (Article 33(3) PCT), because the compounds **29j** and **29k** are either not (**29j**) or very poor (**29k**) vasodilatating compounds (see Table V, page 768: the Coronary dilator potency of these compounds is nil or very low (0.13)). Therefore, the application overcomes a technical prejudice by using pyrazole substituted adenosines as vasodilatating agents, and the subject-matter of claim 1 is considered inventive (Article 33(3) PCT).

6. **Claims 2 to 17 and 19** are dependent on claim 1 and as such also meet the requirements of the PCT with respect to **novelty** and **inventive** step.

7. A method using these new and inventive compounds, or a pharmaceutical composition comprising them is considered new and inventive.

Therefore, the subject-matter of **claims 20 to 25** is considered **new** (Article 33(2) PCT) and **inventive** (Article 33(3) PCT).

8. The compounds disclosed in claims 1-17 and 19 have an application as being comprised in a pharmaceutical composition (claims 23-25).

Therefore, the subject-matter of **claims 1-17, 19 and 23-25** complies with the requirements of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document **D1** is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

1. **Claims 3 to 17** are not supported by the description as required by Article 6 PCT, for the following reasons:

1.1 The features of claims 3 to 6, 8, 12 to 14, 16 and 17, that R^3 is selected from

said particular groups disclosed in said claims, is not referred to in the description.

1.2 The features of claims 3 to 5 that R^5 and R^6 are selected from said particular groups disclosed in said claims, is not referred to in the description.

1.3 The features of claims 3 to 11 and 13 to 16, that R^7 is selected from said particular groups disclosed in said claims, is not referred to in the description.

1.4 The features of claims 8, 13 and 14, that R^8 is selected from said particular groups disclosed in said claims, is not referred to in the description.

2. **Claim 1** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined:

the substituent $\mathbf{R^{23}}$ is not defined in said claim (see claim 1, page 1 of the claim, lines 7, 14 and 25, and page 2 of the claim, lines 11 and 23).

3. The description does not meet the requirements of **Article 5 PCT** in that the invention is not clearly defined: the substituent $\mathbf{R^{23}}$ is not defined (see page 4, lines 9 and 16, and see page 5, lines 1, 13 and 25) in the description. This cannot be considered as an obvious spelling mistake (the substituents R^{20} and R^{22} for instance have different meanings (see from page 5, line 31 to page 6, line 7), the description gives therefore obviously the impression that R^{23} would have yet another meaning).

4. The expression "**and $\mathbf{C_{1\text{-}6}}$**" used in **claim 5** is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers; thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). (It is obvious that "**$\mathbf{C_{1\text{-}6}}$ alkyl**" is meant here, according to the definition of R^5 and R^6 in claim 1).

5. The expression "alkyl or aryl or heteroaryl amide" used in **claim 1** (see the definitions of R^3, R^5, R^6, R^7, R^8, R^{20} and R^{22}) is unclear (the description on page 5, line 5 suggests that "alkylamide, arylamide and heteroarylamide" are meant here) and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

6. **Claim 18** is vague and unclear (according to claim 10, R^1 is CH_2OH, it cannot be at the same time CONHEt) and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

7. **Claim 20** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved ("a therapeutically effective amount ... sufficient to ...") which merely amounts to a statement of the underlying problem.

8. The expressions "for stimulating coronary vasodilatation in a mammal" and "for the purpose of imaging the heart" used in **claim 20** are vague and unclear (Is the method claimed a method of imaging the heart?, or a method for stimulating coronary vasodilatation in a mammal?) and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

9. The use of the expression "*incorporated by reference*" (page 34, line 11 and page 37, line 12) is not allowed in some designated Contracting States.

10. The embodiments of the invention described on page 18, lines 3-14 ("This invention also includes pro-drugs...") do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

11. Attention is drawn to the following spelling mistakes:

Claim 12: "$\mathbf{R_3}$ is",
Claim 13: the "**;**" between "and aryl" and "that is",
page 4, line 18, page 5, lines 3, 15 and 27: "**substituted**",
page 6, line 3: "$_{C2\text{-}15}$",
page 6, line 20: "substituent **that** is",
page 7, line 6: "from **of**",
page 7, line 10: "aryl **in** that **aryl** is",
page 7, line 17: "$C_{1\text{-}3}$ and",
page 20, line 7: "heated **heated**",
page 22, line 15: "The mixture heated" and "at 65°C **in** for 24 h.",
page 26: There is no **Example 12** disclosed,
page 23, line 5: "dissolved one equivalent of",
page 31, line 4: "potency Compound 16" and "and compare**d**".

(MBHB Case No. 99,423-A)

TITLE: N-Pyrazole A_{2A} Receptor Agonists

Background Of The Invention

Field of Invention

This invention includes N-pyrazole substituted 2-adenosine compounds that are useful as A_{2A} receptor agonists. The compounds of this invention are vasodilating agents that are useful as heart imaging aids that aid in the identification of mammals, and especially humans who are suffering from coronary disorders such poor coronary perfusion which is indicative of coronary artery disease (CAD). The compounds of this invention can also be used as therapeutics for coronary artery disease as well as any other disorders mediated by the A_{2A} receptor.

Description of the Art

Pharmacological stress is frequently induced with adenosine or dipyridamole in patients with suspected CAD before imaging with T1 scintigraphy or echocardiography. Both drugs effect dilation of the coronary resistance vessels by activation of cell surface A_2 receptors. Although pharmacological stress was originally introduced as a mean of provoking coronary dilation in patients unable to exercise, several studies have shown that the prognostic value of ^{201}T1 or echocardiographic imaging in patients subjected to pharmacological stress with adenosine or dipyridamole was equivalent to patients subjected to traditional exercise stress tests. However, there is a high incidence of drug-related adverse side effects during pharmacological stress imaging with these drugs such as headache and nausea, that could be improved with new therapeutic agents.

Adenosine A_{2B} and A3 receptors are involved in a mast cell degranulation and, therefore, asthmatics are not give the non-specific adenosine agonists to induce a pharmacological stress test. Additionally, adenosine stimulation of the A_1 receptor in the atrium and A-V node will diminish the S-H interval which can induce AV block (N.C. Gupto et al.; *J. Am Coll. Cardiol;* (1992) 19: 248-257). Also, stimulation of the adenosine A_1 receptor by adenosine may be responsible for the nausea since the A_1 receptor is found in the intestinal tract (J. Nicholls et al.; *Eur. J. Pharm.*(1997) 338(2) 143-150).

Animal data suggests that specific adenosine A_{2A} subtype receptors on coronary resistance vessels mediate the coronary dilatory responses to adenosine, whereas subtype A_{2B} receptor stimulation relaxes peripheral vessels (note: the latter lowers systemic blood

pressure). As a result there is a need for pharmaceutical compositions that are A_{2A} receptor agonists that have no pharmacological effect as a result of stimulating the A_1 receptor *in vivo*. Furthermore, there is a need for A_{2A} receptor agonists that have a short half-life, and that are well tolerated by patients undergoing pharmacological coronary.stress evaluations.

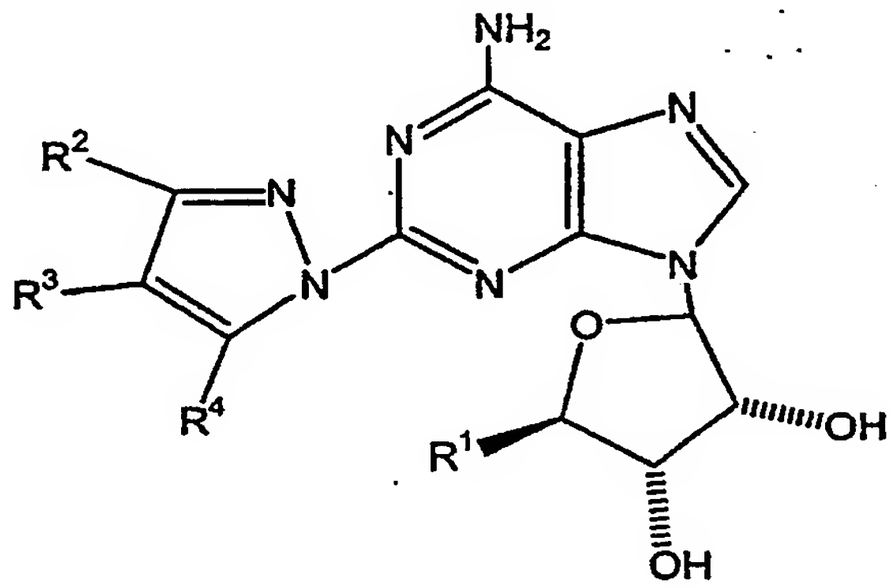
SUMMARY OF THE INVENTION

In one aspect, this invention includes 2-adenosine N-pyrazole compounds that are useful A_{2A} receptor agonists.

In another aspect, this invention includes pharmaceutical compounds including 2-adenosine N-pyrazole that are well tolerated with few side effects.

Still another aspect of this invention are N-pyrazole compounds that can be easily used in conjunction with radioactive imaging agents to facilitate coronary imaging.

In one embodiment, this invention includes 2- adenosine N-pyrazole compounds having the following formula:



In another embodiment, this invention includes methods for using compounds of this invention to stimulate coronary vasodilatation in mammals, and especially in humans, for stressing the heart induced steal situation for purposes of imaging the heart.

In still another embodiment, this invention is a pharmaceutical composition comprising one or more compounds of this invention and one or more pharmaceutical excipients.